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Pyrrolderivate

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(56) References cited:
EP-A- 0 287 890
EP-A- 0 300 249
EP-A- 0 330 172
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Description

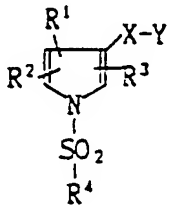
The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

As the first generation of drugs for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, there are known Mevinolin (U.S. Pat.No.4,231,938), pravastatin (JP Unexamed. Pat.Publn.No.59-48418), and simvastatin (U.S. Pat.No.4,444,784), which are fungal metabolites or their chemical modifications. Recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (F.G.kathawala et al, 8th Int'l Symp. on Atherosclerosis, Abstract Papers, p.445, Rome (1988)) and BMY 22089 (GB Pat.No.2,202,846) are developed as the second generation drugs (Pharmacia, the science of the drug, vol.26, No.5 p.453-454, 1990)).

In EP-A-0 300 249, WO 87/02662, EP-A-0 330 172 and EP-A- 0 287 890 pyrrole derivatives are disclosed which are inhihitors of the HMG-CoA reductase enzyme. EP-A-0 287 890 generically discloses an alkylsulphonyl or arylsulphonyl substituent at the N-position of the pyrrole ring.

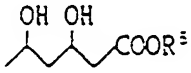
The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Furthermore, the compounds of this invention inhibit the HMG-CoA reductase, which plays a main role in the synthesis of cholesterol, and subsequently they suppress the synthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

The present invention relates to compounds of the formula:

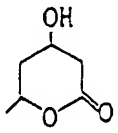


(I)

wherein R^1, R^2, and R^3 each is independently hydrogen, optionally substituted lower alkyl, or optionally substituted aryl whereby one of the substituents R^1, R^2 and R^3 is isopropyl; R^4 is lower alkyl, aralkyl, aryl, or heteroaryl, each of which is optionally substituted; X is vinylene or ethylene; Y is



or



where R^5 is hydrogen, lower alkyl, aryl, aralkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt.

In the specification, the term "lower alkyl" refers to a straight or branched chain C_1 to C_6 alkyl, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, 2-methylbutyl, n-hexyl, isohexyl and the like. Further, the lower alkyl may be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, lower alkoxyamino and cyano.

The term "aryl" refers to C_6 to C_{12} aromatic group including phenyl, tolyl, xylyl, biphenylyl, naphtyl, and the like. The aryl may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano. Preferred aryls are phenyl, biphenylyl, or naphthyl having 1 to 3 substituents selected from the group consisting of lower alkyl and halogen.

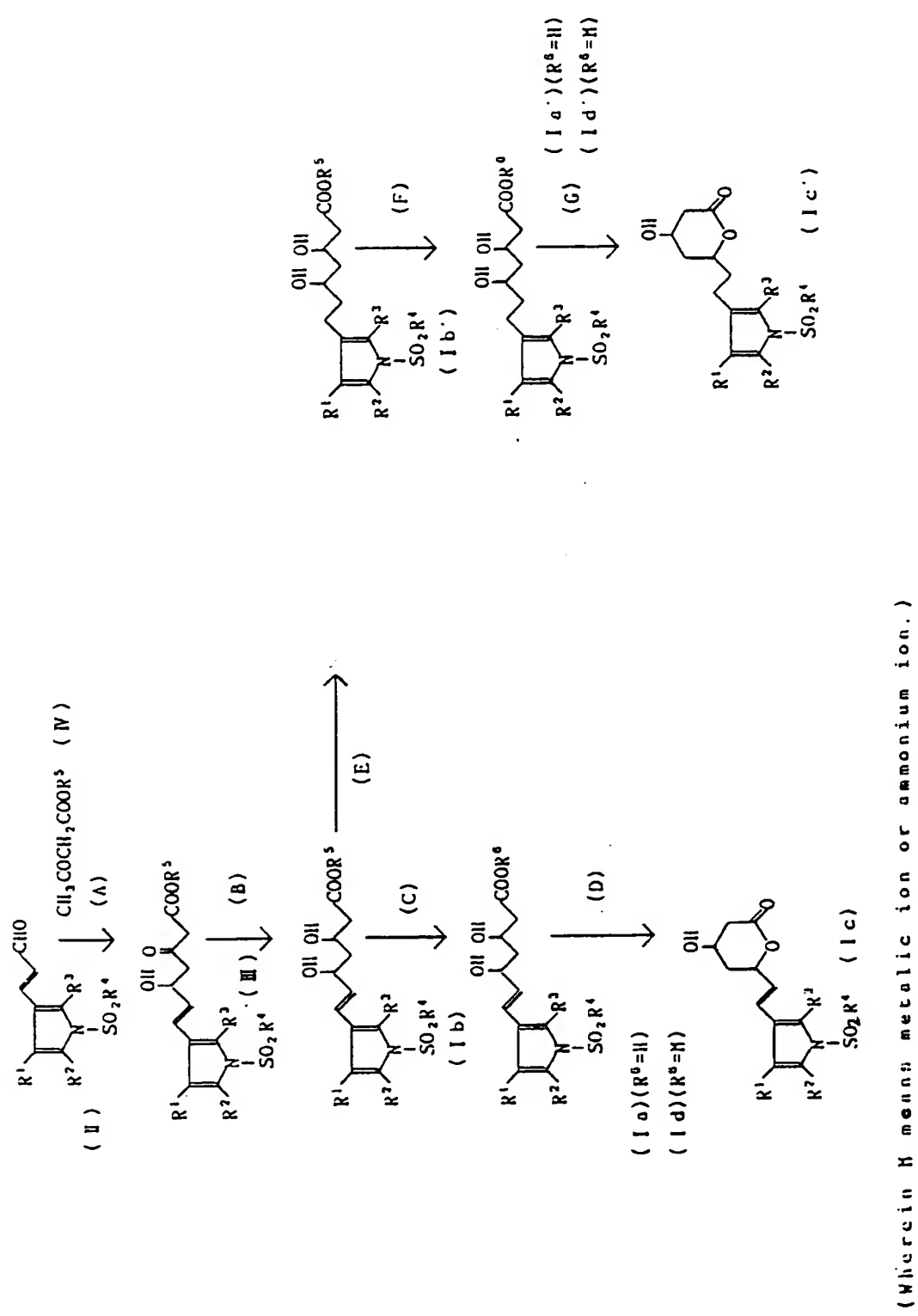
The term "aralkyl" refers to the above-mentioned alkyl substituted by the above-mentioned aryl at an optional position. Examples of them are benzyl, phenethyl, phenylpropyl and the like. The aralkyl may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, cyano, and the like.

The term "heteroaryl" refers to a 5- or 6-membered heterocyclic group containing 1 or 2 atoms selected from the group consisting of oxygen, sulfur, and nitrogen, which may be condensed with a 5- or 6-membered aromatic group. Examples of them ar thienyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, benzothienyl, indolyl, and the like, preferably thienyl, quinolyl, and benzothienyl. Further the group may have 1 to 3 substituents selected from the group consisting of lower alkyl, halogen, amino, and cyano.

The term "halogen" refers to fluorine, chlorine, bromine, and iodine.

The term "a cation capable of forming a non-toxic pharmaceutically acceptable salt" refers to an alkali metal ion, alkaline earth metal ion and ammonium ion. Examples of an alkali metal are lithium, sodium, potassium, and cesium, and examples of an alkaline earth metal are beryllium, magnesium, and calcium. Prefered are sodium and potassium.

The compounds of the present invention can be prepared by the following method.



STEP A

The compound (II) in an organic solvent is added dropwise to a dianion organic solution, which is prepared from sodium hydride and butyllithium, of the compound (IV), if necessary under nitrogen atmosphere to give the compound (III).

The reaction is performed preferably under cooling at -80 to 0 °C, for 10 minutes to 10 hours, preferably 30 minutes to 3 hours.

Organic solvents which may be used are ethers such as diethylether and tetrahydrofuran, dimethylformamide, acetonitrile, and the like, most preferably tetrahydrofuran.

STEP B

The compound (III) is treated with diethylmethoxyborane and $NaBH_4$ in alcoholic organic solvent under cooling, then the reaction mixture is chromatographed on silica gel to give the compound (Ib).

The reaction is performed under cooling at -80 to 0 °C, for 5 minutes to 5 hours, preferably for 30 minutes to 2 hours.

Alcohols which may be used are methanol, ethanol, propanol, butanol, and the like.

The same organic solvents as in STEP A may be used.

STEP C

The compound (Ib) is hydrolyzed, then neutralized with acid, and extracted with an organic solvent to give the compound (Ia). Alternatively, after the hydrolysis, the reaction mixture is evaporated under reduced pressure and freeze-dried to give the compound (Id).

The hydrolysis is performed in the ordinary method in the solvents such as water, alcohols, dioxane, acetone, or their mixture, preferably in the presence of a base.

The reaction temperature is 0 to 50°C, preferably at near room temperature.

The base may be sodium hydroxide, potassium hydroxide, or their analogue.

The acids mean inorganic acids such as hydrochloric acid, sulfuric acid, and the like.

STEP D

The compound (Ia) or (Id) is refluxed in an organic solvent, if necessary under heating to give the compound (Ic).

The reaction is performed for 1 to 10 hours, preferably for 3 to 5 hours, under heating.

Organic solvents which may be used are the same solvents as in Step A, benzene, toluene, dichlorethane, and the like.

The compound (Ic) is alternatively prepared by the left of the compound (Ia) or (Id) at room temperature for 50 to 100 days. However this procedue needs long term, usually the former procedure is adopted.

STEP E

The compound (Ib') is prepared by the reduction of the compound (Ib).

The reaction is performed in an appropriate inactive solvent in the presence of the catalyst for the catalytic reduction at 10 to 50°C, preferably at near room temperautre, for 30 minutes to 10 hours, preferably for 5 to 7 hours.

Inactive solvents which may be used are water, acetic acid, methanol, ethanol, dioxane, and the like.

The catalysis of the catalytic reduction which may be used are platinum-carbon, palladium-carbon, radium-carbon, and the like, most preferably palladium-carbon.

STEP F

The compound (Ib') is reacted in the same manner as in Step C to give the compound (Ia') or (Id').

STEP G

The compound (Ia') or (Id') is reacted in the same manner as in Step D to give th⁻ compound (Ic').

The compound of the present invention can be administered orally or parenterally. For example, the compounds of the present invention may be orally administered in the form of tablets, powders, capsules, and granules, aqueous or oily suspension, or liquid form such as syrup or elixir, and parenterally in the form of injection of aqueous or oily suspension.

These preparations can be prepared in a conventional manner by using excipients, binders, lubricants, aqueous or oily solubilizers, emulsifier, suspending agents, and the like. Furthermore preservatives and stabilizers can be used.

The dosages may vary with the administration route and age, weight, conditions, and the kind of disease of the patients, but usually are 0.05-500 mg/day, preferably 0.5-200 mg/day for oral administration, and 0.01-200 mg/day, preferably 0.1-100 mg/day for parenteral administration in a single or divided doses.

The present invention is illustrated by the following examples and reference examples.

The abbreviations used in examples and reference examples have the following meanings.

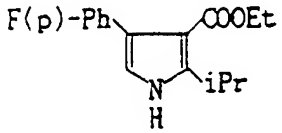
Me : methyl, Et : ethyl, i-Pr : isopropyl

Ph : phenyl, DMF : dimethylformamide, Bz : benzyl

THF : tetrahydrofuran, TFA : trifluoroacetic acid

Example 1

(1) Ethyl 4-(4-fluorophenyl)-2-isopropylpyrrole-3-carboxylate 1

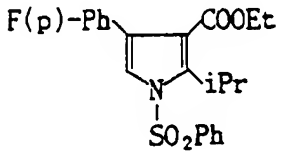


A mixture of 6.85 g (43.3 mmol) of ethyl isobutyrylacetate, 10.69 g (56.3 mmol) of 2-amino-4'-fluoracetophenone hydrochloride, 16.3 ml of acetic acid, 6.04 g of sodium acetate, and 10.8 ml of water is refluxed for 4 hours. After cooling, the reaction mixture is adjusted to pH 8 with saturated $NaHCO_3$ and extracted with ether. The extract 8.36 g is subjected to column chromatography (silica gel), eluting with methylene chloride to give 6.12 g (Yield : 51.3%) of the compound 1.

NMR ($CDCl_3$) δ :

1.14 (t, 3H, J=7Hz); 1.31 (d, 6H, J=7Hz); 3.81 (septet, 1H, J=7Hz); 4.15 (q, 2H, J=7Hz); 6.58 (d, 1H, J=2.4Hz); 6.96-7.05 (m, 2H); 7.29-7.37 (m, 2H); 8.36 (brs, 1H)

(2) Ethyl 4-(4-fluorophenyl)-2-isopropyl-1-phenylsulfonylpyrrole-3-carboxylate 2

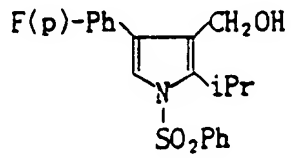


To a suspension of 948 mg (23.7 mmol) of 60% NaH in 50 ml of anhydrous DMF a solution of 5.93 g (21.5 mmol) of compound 1 in 60 ml of anhydrous DMF is added dropwise under a nitrogen atmosphere. The reaction mixture is stirred for 30 minutes while cooling with ice. To the mixture a solution of 4.18 g (23.7mmol) of benzene-sulfonyl chloride in 10 ml of anhydrous DMF is added dropwise and the mixture is stirred at room temperature for 2 hours and mixed with ice-water. The solution is extracted with ether, and the organic layer is washed with water to give 9.65 g of an oil. It is subjected to column chromatography (silica gel), eluting with n-hexane/methylene chloride (1 /2) to give 8.65 g (Yield : 96.6 %) of the compound 2.

NMR ($CDCl_3$) δ :

1.10 (t, 3H, J=7Hz); 1.14 (d, 6H, J=7Hz); 3.57 (septet, 1H, J=7Hz); 4.13 (q, 2H, J=7Hz); 7.00-7.10 (m, 2H); 7.26-7.33 (m, 2H); 7.35 (s, 1H); 7.52 -7.71 (m, 3H); 7.82-7.86 (m, 2H)

(3) 4-(4-Fluorophenyl)-3-hydroxymethyl-2-isopropyl-1-phenylsulfonylpyrrole 3

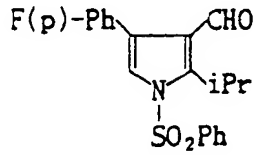


To a solution of 4.16 g (10 mmol) of compound 2 in 200 ml of anhydrous toluene 25ml of 1M · DIBAL in touluene is added dropwise under nitrogen atmosphere at -65 to -70 °C for 15 minutes. The reaction mixture is stirred at the same temperature for 1 hour. To the reaction mixture water and 10 % hydrochloric acid are added. The mixture is warmed up to room temperature and extracted with ether. The insoluble material is filtered off on celite. The ether layer is washed with water, dried and concentrated under reduced pressure to give 4.03 g (Yield : 107.6%, containing the solvent) of compound 3.

NMR ($CDCl_3$) δ :

1.17 (d, 6H, J=7Hz); 3.61 (septet, 1H, J=7Hz); 4.53 (d, 2H, J=4.7Hz); 7.05-7.15 (m, 2H); 7.41 (s, 1H); 7.50-7.68 (m, 5H); 7.79-7.84 (m, 2H)

(4) 4-(4-Fluorophenyl)-3-formyl-2-isopropyl-1-phenylsulfonylpyrrole 4

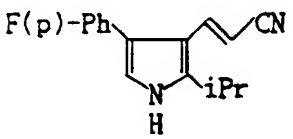


A mixture of 4.03 g (10.8 mmol) of compound 3, 4.36 g (32.4 mmol) of N-methylmorpholine-N-oxide, 81 mg (0.23 mmol) of tetrapropylammonium perruthenate (TPAP), 20 g of powdered molecular sieves 4A, and 150 ml of methylene chloride is stirred at room temperature for 2 hours, and the insoluble material is filtered off on celite. The filtrate is concentrated to one-fifth of its original volume under reduced pressure. It is subjected to column chromatography, (silica gel) eluting with methylene chloride to give 3.67 g (Yield : 91.2%) of compound 4.

NMR ($CDCl_3$) δ :

1.16 (d, 6H, J=7Hz); 3.715 (septet, 1H, J=7Hz); 7.05-7.14 (m, 2H); 7.34-7.41 (m, 3H); 7.56-7.71 (m, 3H); 7.86-7.90 (m, 2H); 10.01 (s, 1H)

(5) β-[4-(4-fluorophenyl)-2-isopropylpyrrol-3-yl]-(E)-acrylonitrile 5



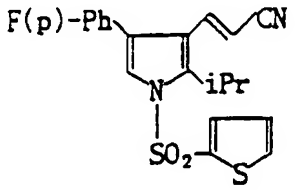
To a suspension of 631 mg (15.8 mmol) of 60% NaH in anhydrous THF a soluti n of 2.62 g (14.8 mmol) of diethyl cyanomethylphosphonate in 15 ml of anhydrous THF is added dropwise under nitr gen atm sphere for 1 hour. The reaction mixture is stirred at the same temperature for 30 minutes. A solution of 3.67 g (9.85 mmol) of the compound 4 in 40 ml of anhydrous THF is added thereto for 45 minutes. The mixture is warmed up to room temperature and mixed with ice-water. The solution is extracted with ether, washed with water, and concentrated under reduced pressure to

give 4.71 g of oil. To a solution of this oil in a mixture of 30 ml of THF and 100 ml of methanol 20 ml of 10% NaOH is added, and the mixture is stirred at 50°C for 1 hour. The mixture is neutralized with 10 % HCl, extracted with methylene chloride, washed with water, and concetrated under reduced pressure. The obtained 2.84 g of crude crystals are purified by column chromatography, (silica gel) eluting with methylene chloride to give 2.11 g (Yi ld : 84.2%) of crystalline compound 5.

NMR ($CDCl_3$) δ :

1.32 (d, 6H, J=7Hz); 3.24 (septet, 1Hz, J=7Hz); 5.09, 7.36 (ABq, 2H, J= 16,6Hz); 6.62 (d, 1H, J=2.4Hz); 7.03-7.13 (m, 2H); 7.23-7.33 (m, 2H); 8.24 (br, 1H)

(6) β-[4-(4-Flurophenyl)-2-isopropyl-1-(2-thiophenesulfonyl)pyrrol-3-yl]-(E)-acrylonitrile 6

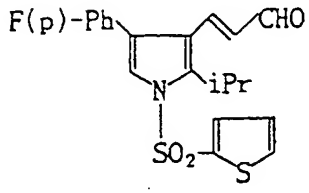


To a suspension of 48 mg (1.2 mmol) of 60% NaH in 4 ml of anhydrous DMF a solution of 256 mg (1 mmol) of compound 5 in 3 ml of anhydrous DMF is added dropwise under nitrogen atmosphere for 5 minutes. The reaction mixture is stirred at the same temperature for 30 minutes, and a solution of 201 mg (1.1 mmol) of 2-thiophenonesulfonyl-chloride in 3 ml of anhydrous DMF is added dropwise thereto for 5 minutes. The reaction mixture is warmed up to room temperature and stirred for 3 hours. To the mixture ice-water is added and the solution is extracted with ether, washed with water, and concentrated under reduced pressure to give 413 mg (Yield : 103%) of compound 6 as crude crystals.

NMR ($CDCl_3$) δ :

1.26 (d, 6H, J=7Hz); 3.86 (septet, 1H, J=7Hz); 4.93,7.47 (ABq, 2H, J=16, 6Hz); 7.05-7.30 (m, 6H); 7.34-7.78 (m, 2H)

(7) 3-[4-(4-fluorophenyl)-2-isopropyl-1-(2-thiophenesulfonyl)pyrrol-3-yl]-(E)-propenal (II-1)

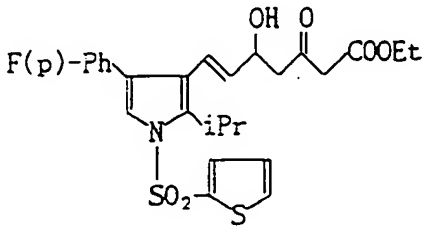


To a solution of 408 mg (1.02 mmol) of the compound 6 in 15 ml of anhydrous THF 3.6 ml of 1M-DIBAL in toluene is added dropwise under nitrogen atmosphere for 5 minutes, and the reaction mixture is stirred at room temperature for 2 hours. To the mixture ice and then saturated NaH_2PO_4 are added, and the mixture is extracted with methylene chloride. The insoluble material is filtered off on celite. The organic layer is concentrated under reduced pressure, and the residue is subjected to column chromatography (silica gel) to give 225 mg (Yield : 54.6%) of the compound (II-1).

NMR ($CDCl_3$) δ :

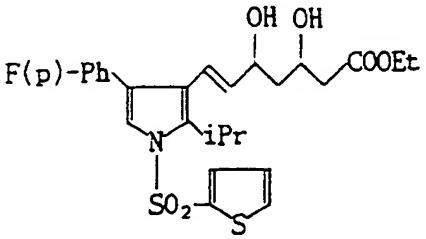
1.31 (d, 6H, J=7Hz); 3.92 (septet, 1H, J=7Hz); 5.83 (dd, 1H, J=16, 8Hz); 7.02-7.29 (m, 6H); 7.58 (d, 1H, J=16Hz); 7.76 (d, 2H, J=4Hz); 9.44 (d, 1 H, J=8Hz)

(8) Ethyl 7-[4-(4-fluorophenyl)-2-isopropyl-1-(2-thiophenesulfonyl)pyrrol-3-yl]-5-hydroxy-3-oxo-(E)-6-heptenate (III-1)



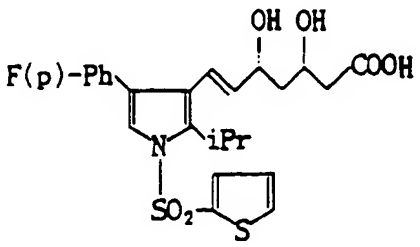
To a suspension of 72 mg (1.80 mmol) of 60% NaH in 5 ml of anhydrous THF a solution of 234 mg (1.80 mmol) of ethyl acetoacetate in 5 ml of anhydrous THF is added dropwise under nitrogen atmosphere while cooling with ice for 5 minutes. The reaction mixture is stirred at the same temperature for 30 minutes and 1.02 ml (1.64 mmol) of 1.6M-nBuLi in n-hexane is added dropwise thereto for 5 minutes. The reaction mixture is stirred for further 30 minutes, and a solution of 220 mg (0.545 mmol) of the compound (II-1) in 5 ml of anhydrous THF is added dropwise thereto at - 78°C for 5 minutes. The reaction mixture is stirred for further 2 hours and poured into a mixture of acetic acid and ice. The mixture is adjusted to pH 8 with $NaHCO_3$, and extracted with ether. The organic layer is washed with water and concentrated under reduced pressure to give 0.41 g of an oil. It is subjected to column chromatography (silica gel) eluting with methylene chloride/ethyl acetate (20/1) to give 227 mg (Yield : 78.0%) of the compound (III-1).
NMR ($CDCl_3$) δ :
1.22 (d, 6H, J=7Hz); 1.26 (t, 3H, J=7Hz); 2.59-2.67 (m, 2H); 3.42 (s, 2H); 3.74 (septet, 1H, J=7Hz); 4.19 (q, 2H, J=7Hz); 4.57 (m, 1H); 5.23 (dd, 1H, J=16,6Hz); 6.62(dd, 1H, J=16, 1Hz); 7.00-7.32 (m, 6H); 7.67-7.71 (m, 2H)

(9) Ethyl 7-[4-(4-fluorophenyl)-2-isopropyl-1-(2-thiophensulfonyl)pyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ib-1)



To a solution of 220 mg (0.545 mmol) of the compound (III-1) in 6.3 ml of anhydrous THF and 1.6 ml of anhydrous methanol 0.459 ml (0.6 mmol) of 1M-diethylmethoxyborane in THF is added dropwise under nitrogen atmosphere for 5 minutes, and the reaction mixture is stirred at the same temperature for 1 hour. To the mixture 18 mg (0.6 mmol) of $NaBH_4$ is added and the mixture is stirred for 2 hours. The reaction mixture is mixed with 0.5 ml of acetic acid, adjusted to pH8 with saturated $NaHCO_3$ and extracted with ether. The organic layer is washed with water and concentrated under reduced pressure. To the obtained residue methanol is added. The solution is concentrated under reduced pressure. This procedure is repeated 3 times and the obtained residue (210 mg) is subjected to column chromatography (silica gel) eluting with methylene chloride/ethyl acetate (20/1) to give 180 mg (Yield : 80.6%) of compound (Ib-1).
NMR ($CDCl_3$) δ :
1.20-1.30 (m, 9H); 1.40-1.60 (m, 2H); 2.42-2.45 (m, 2H); 3.13 (d, 1H, J= 2Hz); 3.66 (d, 1H, J=3Hz); 3.74 (septet, 1H, J=7Hz); 4.17 (q, 2H, J=7Hz); 4.36 (m, 1H); 5.23 (dd, 1H, J=16, 6Hz)

(10) 7-[4-(4-Fluorophenyl)-2-isopropyl-1-(2-thiophenesulfonyl)pyrrol-3-yl]-3(R*),5(S*)-dihydroxy-(E)-6-heptenoic acid (Ia-1)

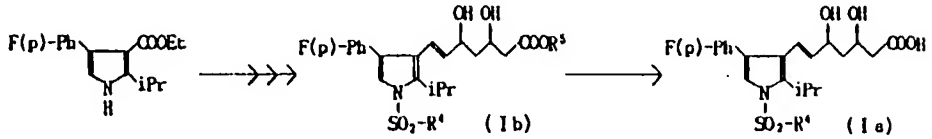


To a solution of 161 mg (0.3 mmol) of compound (Ib-1) in 5 ml of methanol and 0.5 ml of water 0.3 ml (0.6 mmol) of 2N-NaOH is added. The mixture is stirred at room temperature for 1 hour and the pH is adjusted to pH7 with 2N-HCl. The reaction mixture is extracted with methylene chloride, washed with saturated NaCl and concentrated under reduced pressure to give 116 mg (Yield : 76.2%) of compound (Ia-1).
NMR ($CDCl_3$-CD_3OD=7:2) δ :
1.21 (d, 6H, J=7Hz); 1.45 (m, 2H); 2.38-2.40 (m, 2H); 3.73 (septet, 1H, J=7Hz); 4.11 (m, 1H); 4.28 (m, 1H); 5.25 (dd, 1H, J=16,7Hz); 6.54 (d, 1 H, J=16Hz); 6.98-7.38 (m, 6H); 7.68-7.76 (m, 2H)

Example 2-13

The reactions are performed according to the process of Example 1(1) -(10) to give compound (Ia) and (Ib). The physical constants are shown in Table 1, 2, and 3.

Table 1 (No.1)



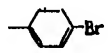
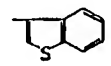
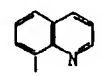
Ex.No.	R⁴	R⁵	I b Yield, NMR ($CDCl_3$)	I a Yield, NMR ($CDCl_3$/CD_3OD=7/2)
2		Et	I b-2 (86.9%) 1.099 (d,3H,J=7Hz); 1.107 (d,3H,J=7Hz); 1.26 (t,3H,J=7Hz); 1.36-1.63 (m,2H); 2.41-2.45(m,2H); 3.07 (d,1H, J=2Hz) 3.55 (septet,1H,J=7Hz); 3.63 (d,1H,J=3Hz); 4.10-4.22 (m, 3H); 4.36 (m,1H); 5.26 (dd,1H,J=16,6Hz); 5.56 (dd,1H,J=16,1Hz); 6.98-7.07 (m,2H); 7.26-7.34 (m,2H); 7.50-7.68 ((m,3H); 7.78-7.83 (m,2H)	I a-2 (90.6%) 1.09 (d,6H,J=7Hz); 1.20-1.65 (m,2H); 2.29 (m,2H) 3.53 (septet,1H,J=7Hz); 4.00 (m,1H); 4.25 (m,1H) 5.24 (dd,1H,J=16,6Hz); 6.50 (d,1H,J=16Hz); 6.98-7.06 (m,2H); 7.28~7.39 (m,2H); 7.53~7.83 (m,5H)
3		Et	I b-3 (79.5%) 1.15 (d,6H,J=7Hz); 1.27 (t,3H,J=7Hz); 1.39-1.63 (m,2H); 2.42-2.45 (m,2H); 3.12 (d,1H,J=2Hz); 3.54 (septet,1H,J=7Hz); 3.63 (d,1H,J=2Hz); 4.10-4.22 (m,3H); 4.36 (m,1H); 5.25 (dd,1H,J=16,6Hz); 6.56 (dd,1H,J=16,1Hz); 6.98-7.07 (m,2H); 7.24-7.33 (m,3H); 7.67 (m,4H)	I a-3 (83.6%) 1.13 (d,6H,J=7Hz); 1.25-1.60 (m,2H); 2.32 (m,2H) 3.53 (septet,1H,J=7Hz); 4.09 (m,1H); 4.26 (m,1H) 5.25 (dd, 1H,J=16,6Hz); 6.51 (d,1H,J=16Hz); 6.98-7.06 (m,2H); 7.25-7.33 (m,2H); 7.36 (s,1H); 7.70 (m,4H)
4		Me	I b-4 (92.7%) 1.24 (d,6H,J=7Hz); 1.30-1.62 (m,2H); 2.42-2.46 (m,2H); 3.70 (s,3H); 3.80 (septet,1H,J=7Hz); 4.16 (m,1H); 4.36 (m,1H); 5.26 (dd,1H,J=16,6Hz); 6.57 (dd,1H,J=16,1Hz); 6.98-7.07 (m,2H); 7.23-7.33 (m,3H); 7.48 (m,2H); 7.83-7.96(m,3H)	I a-4 (95.2%) ($CDCl_3$) 1.23 (d,6H,J=7Hz); 1.30-1.66 (m,2H); 2.49 (d,2H, J=6Hz); 3.80 (septet,1H,J=7Hz); 4.19 (m,1H); 4.37 (m,1H); 5.26 (dd,1H,J=16,6Hz); 6.57 (dd,1H,J=16,1Hz); 6.98-7.07 (m,2H); 7.23-7.32 (m,3H); 7.50 (m,2H); 7.83-7.96 (m,3H)
5		Et	I b-5 (85.2%) 1.052 (d,3H,J=7Hz); 1.076 (d,3H,J=7Hz); 1.26 (t,3H,J=7Hz); 1.38-1.63 (m,2H); 2.42-2.44 (m,2H); 3.10 (brs,1H); 3.60 (septet,brs,2H); 4.11-4.21 (q+brs,3H); 4.35 (m,1H); 5.25 (dd,1H,J=16,6Hz); 5.56 (d,1H,J=16Hz); 6.98-7.07 (m, 2H) 7.27-7.36 (m,2H); 7.51-7.70 (m,3H); 8.10-8.27 (m,3H) 9.02 (m,1H)	I a-5 (63.5%) 1.034 (d,3H,J=7Hz); 1.058 (d,3H,J=7Hz); 1.20-1.65 (m,2H); 2.33-2.36 (m,2H); 3.58 (septet,1H,J=7Hz); 4.08 (m,1H); 4.25 (m,1H); 5.24 (dd,1H,J=16,6Hz); 6.52 (d,1H,J=16Hz); 6.98-7.07 (m,2H); 7.29-7.40 (m,2H); 7.54-7.73 (m,3H); 8.12-8.33 (m,3H); 9.02 (m,1H)

Table 1 (No.2)

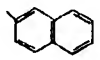
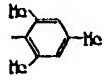
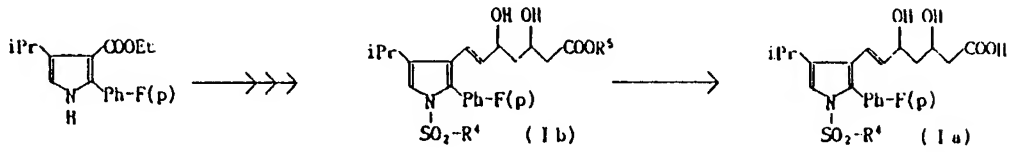
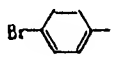
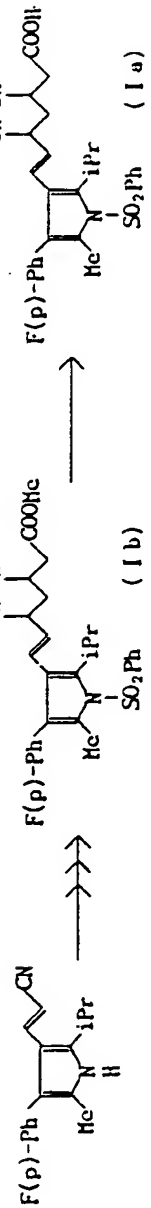
6		Et	I b-6 (84.7%) 1.082 (d,3H,J=7Hz); 1.088 (d,3H,J=7Hz); 1.25 (t,3H,J=7Hz); 1.36-1.62 (m,2H); 2.40-2.43 (m,2H); 3.10 (brs,1H); 3.67 (septet,brs,2H); 4.09-4.20 (q*,brs,3H); 4.34 (brs,1H) 5.25 (dd,1H,J=16,6Hz); 6.54 (dd,J=16,1Hz); 6.98-7.07 (m,2H); 7.26-7.34 (m,3H); 7.63-7.72 (m,3H); 7.89-8.01 (m,3H); 8.46 (d,1H,J=1Hz)	I a-6 (67.8 %) 1.09 (d,6H,J=7Hz); 1.40-1.65 (m,1H); 2.41 (d,2H,J=6Hz); 3.66 (septet,1H,J=7Hz); 4.12 (m,1H); 4.28 (m,1H); 5.26 (dd,1H,J=16,6Hz); 6.53 (d,1H,J=16Hz); 7.01-7.11 (m,2H); 7.30-7.38 (m,3H); 7.66-7.76 (m,3H); 7.93-8.05 (m,3H); 8.48 (d,1H,J=2Hz)
7		Et	I b-7 (82.1%) 0.996 (d,3H,J=7Hz); 1.007 (d,3H,J=7Hz); 1.26 (t,3H,J=7Hz); 1.38-1.63 (m,2H); 2.41-2.44 (m,2H); 3.11 (brs,1H); 3.46 (septet,1H,J=7Hz); 3.65 (d,1H,J=2Hz); 4.11-4.22 (q*brs,3H); 4.34 (m,1H); 5.25 (dd,1H,J=16,6Hz); 6.54 (d,1H,J=16Hz); 7.00-7.09 (m,2H); 7.27-7.36 (m,2H); 7.45 (s,1H) 7.53-7.70 (m,3H); 7.94-7.99 (m,2H); 8.12-8.16 (m,1H); 8.52-8.58 (m,1H)	I a-7 (79.0%) 0.98 (d,6H,J=7Hz); 1.30-1.60 (m,2H); 2.35 (m,2H) 3.45 (septet,1H,J=7Hz); 4.10 (m,1H); 4.25 (m,1H) 5.24 (dd,1H,J=16,6Hz); 6.50 (d,1H,J=16Hz); 7.00-7.09 (m,2H); 7.29-7.38 (m,3H); 7.46 (s,1H); 7.56-7.72 (m,3H); 7.96-8.02 (m,2H); 8.17 (d,1H,J=8Hz); 8.54 (d,1H,J=8Hz)
8		Et	I b-8 (73.1 %) 0.992 (d,3H,J=7Hz); 1.004 (d,3H,J=7Hz); 1.27 (t,3H,J=7Hz); 1.40-1.63 (m,2H); 2.32 (s,3H); 2.42-2.46 (m,2H); 2.48 (s,6H); 3.04 (septet,1H,J=7Hz); 3.64 (d,1H,J=2Hz); 4.11-4.19 (q*brs,3H); 4.35 (brs,1H); 5.26 (dd,1H,J=16,6Hz); 6.56 (dd,1H,J=16,1Hz); 6.96-7.06 (m,4H); 7.26-7.33 (m,3H)	I a-8 (100 %) 1.01 (d,6H,J=7Hz); 1.40-1.65 (m,2H); 2.34 (s,3H) 2.43 (d,2H,J=6Hz); 2.49 (s,6H); 3.08 (septet,1H,J=7Hz); 4.12 (m,1H); 4.28 (m,1H); 5.27 (dd,1H,J=16,6Hz); 6.55 (d,1H,J=16Hz); 7.00-7.08 (m,4H); 7.26-7.44 (m,3H)
9		Et	I b-9 (82.3 %) 0.983 (d,3H,J=7Hz); 0.995 (d,3H,J=7Hz); 1.27 (t,3H,J=7Hz); 1.35-1.63 (m,2H); 2.42-2.47 (m,2H); 3.05-3.27 (m,2H); 3.67 (d,1H,J=2Hz); 4.12-4.22 (q*brs, 3H); 4.36 (m,1H); 5.20 (dd,1H,J=16,6Hz); 6.18 (s,1H); 6.54 (d,1H,J=16Hz); 6.92-7.32 (m,10H); 7.54-7.70 (m,2H); 8.17 (m,1H)	I a-9 (94.7%) 1.01 (d,6H,J=7Hz); 1.40-1.70 (m,2H); 2.44 (d,2H,J=6Hz); 3.16 (septet,1H,J=7Hz); 4.13 (m,1H); 4.33 (m,1H); 5.22 (dd,1H,J=16,6Hz); 6.18 (s,1H); 6.52 (d,1H,J=16Hz); 6.94-7.44 (m,10H); 7.66 (m,2H) 8.15-8.20 (m,1H)
10	M e	Et	I b-10 (79.3%) 1.28 (t,3H,J=7Hz); 1.41 (d,6H,J=7Hz); 1.48-1.75 (m,2H); 4.55 (m,2H); 3.22 (s,3H); 3.67 (septet,1H,J=7Hz); 4.18 (q,2H,J=7Hz); 4.29 (brs,1H); 4.41 (brs,1H); 5.31 (dd,1H,J=16,6Hz); 6.64 (dd,1H,J=16,1Hz); 7.02 (m,2H); 7.28 (m,2H)	I a-10 (87.8%) 1.41 (d,2H,J=7Hz); 1.50-1.70 (m,2H); 2.53 (d,2H,J=6Hz); 3.22 (s,2H); 3.67 (septet,1H,J=7Hz); 4.25 (m,1H); 4.44 (m,1H); 5.31 (dd,1H,J=16,6Hz); 6.64 (d,1H,J=16Hz); 7.05 (m,2H); 7.28 (m,2H)

Table 2



Ex.No.	R^4	R^5	(I) (g, %, °C)	Anal Calcd. (%) for :	
11		Me	I b-11 0.35 g (94.3%) 64~65°C I a-11 0.27 g (93.8%) 104°C~	I b-11 ($C_{31}H_{31}NSBrFO_4$) : C,54.55; H,4.92; N,2.36; S,5.39 Br,13.44; F,3.20 Found : C,54.98; H,5.16; N,2.62; S,5.48 Br,13.73; F,3.84	I a-11 ($C_{31}H_{31}NSBrFO_4 \cdot 0.25Et_2O$) : C,54.14; H,4.96; N,2.34; S,5.35 F,3.17 Found : C,54.40; H,5.02; N,2.39; S,5.41 F,2.87
12		Me	I b-12 0.51 g (94.1%) I a-12 0.28 g (92.7%) 45 °C~	I b-12 ($C_{31}H_{32}NS_2FO_4$) : C,57.57; H,5.41; N,2.69; S,12.29 F,3.64 Found : C,57.07; H,5.56; N,2.68; S,12.23 F,3.86	I a-12 ($C_{31}H_{32}NS_2FO_4$) : C,56.79; H,5.16; N,2.76; S,12.63 F,3.74 Found : C,56.56; H,5.33; N,2.86; S,12.73 F,3.73



(I b)

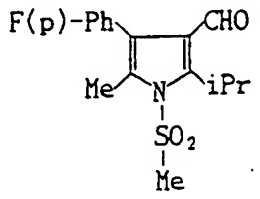
(I a)

Table 3

Ex.No.	(I) (g, %, °C)	Anal Calcd. (%) for:	
13	I b-13 I a-13 0.34 g 0.17 g (89.5%) (83.3%) 101~103°C	I b-13 ($C_{3}H_{3}NSFO_{4}$) : C,63.50; H,6.09; N,2.64; S,6.05 F,3.59 Found : C,63.37; H,6.02; N,2.60; S,6.14 F,3.89	I a-13 ($C_{3}H_{3}NSFO_{4}$) : C,62.90; H,5.87; N,2.72; S,6.22 F,3.68 Found : C,62.53; H,6.07; N,2.99; S,6.08 F,3.48

Example 14

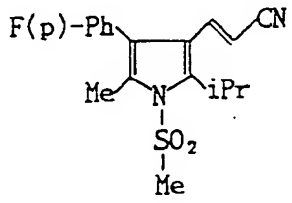
(1) 4-(4-Fluorophenyl)-3-formyl-2-isopropyl-5-methyl-1-methylsulfonylpyrrole 7



As starting material, a mixture of 6.33 g (40 mmol) of ethyl isobutyrylacetate, 12.22 g (60 mmol) of 2-amino-4'-fluoropropiophenone-hydrochloride, 1 ml of acetic acid, 5.58 g of sodium acetate, and 0.7 ml of water is reacted according to the process of Example 1 (1) to (4) to give 1.42 g (Yield : 79.8%) of compound 7. mp .126-127 °C

Anal Calcd. (%) for $C_{16}H_{18}NSFO_3$					
	C, 59.43;	H, 5.61;	N, 4.33;	S, 9.91;	F, 5.87
Found	C, 59.43;	H, 5.60;	N, 4.32;	S, 10.13;	F, 5.58

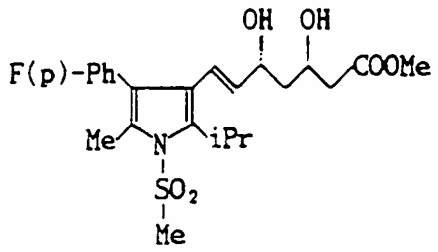
(2) β-[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-1-methylsulfonylpyrrol-3-yl]-(E)-acrylonitrile 8



To a suspension of 0.77 g of 60% NaH in 40 ml of THF a solution of 1.70 g (9.6 mmol) of diethyl cyanomethylphosphonate in 10 ml of THF is added dropwise while cooling with ice. The mixture is stirred for 45 minutes. To the mixture a solution of 2.07 g (6.4 mmol) of compound 7 in 30 ml of THF, is added dropwise. The mixture is stirred for 2 hours and mixed with ice-water. The solution is extracted with ether and washed with water. The ether layer is dried over Na_2SO_4 and evaporated under reduced pressure. The residue is subjected to column chromatography (silica gel), eluting with hexane-ether (1/2) to give 0.58 g (Yield : 26.1%) of compound 8. Recrystallization from ether gives the crystals melting at 137-139°C.

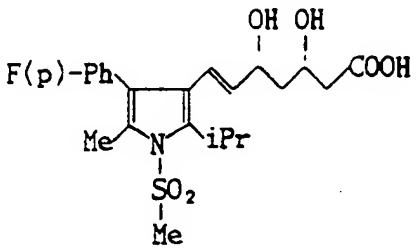
Anal Calcd. (%) for $C_{18}H_{19}N_2SFO_2$					
	C, 62.41;	H, 5.53;	N, 8.09;	S, 9.25;	F, 5.48
Found	C, 62.55;	H, 5.56;	N, 8.07;	S, 9.39;	F, 5.78

(3) Methyl 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-methylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ib-14)



Compound 8 is reacted according to the process of Example 1 (7) to (9) to give 0.25 g (Yield : 99.6%) of compound (Ib-14) as a syrup.
NMR ($CDCl_3$) δ :
1.39 (d, J=7Hz, 6H); 2.24 (s, 3H); 2.44 (d, J=7Hz, 2H); 3.18 (s, 3H); 3.72 (s, 3H); 3.84 (m, 1H); 4.31 (m, 1H); 5.01 (dd, J=16,6Hz, 1H); 6.57 (dd, 16,1Hz, 1H); 7.10 (m, 4H)

(4) 7-[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-1-methylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenoic acid (Ia-14)

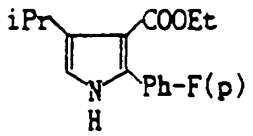


Compound (Ib-14) 0.12 g (0.26 mmol) is reacted according to Example 1 (10) to give 0.1 g (Yield : 84.7%) of compound (Ia-14) as a powder.
NMR ($CDCl_3$) δ :
1.37 (d, J=7Hz, 6H); 2.24 (s, 3H); 2.50 (d, J=6Hz, 2H); 3.18 (s, 3H); 3. 84 (m, 1H); 4.17 (m, 1H); 4.33 (m, 1H); 5.10 (dd, J=16,6Hz, 1H); 6.57 (dd, J=16,1Hz, 1H); 7.12 (m, 4H)

Anal Calcd. (%) for $C_{22}H_{28}NSFO_6 \cdot 0.25H_2O$				
	C, 57.69;	H, 6.27;	N, 3.06;	S, 7.00
Found	C, 57.57;	H, 6.30;	N, 3.04;	S, 6.71

Example 15

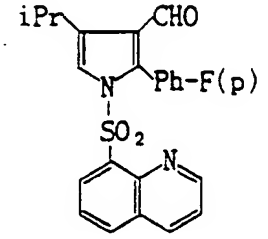
(1) Ethyl 4-isopropyl-2-(4-fluorophenyl)pyrrole-3-carboxylate 9



A mixture of 9.91 g (72.0 mmol) of 3-methyl-2-oxobutylamine-hydrochloride, 12.6 g (59.9 mmol) of ethyl 4-fluorobenzoate, 8.37 g of sodium acetate, 22.8 ml of acetic acid, and 15.6 ml of water is reacted according to Example 1 (1) to give 9.06 g (Yield : 54.9 %) of compound 9. mp. 108-109 °C

Anal Calcd. (%) for $C_{16}H_{18}NFO_2$				
	C, 69.80;	H, 6.59;	N, 5.09;	F, 6.90
Found	C, 69.84;	H, 6.61;	N, 5.18;	F, 6.72

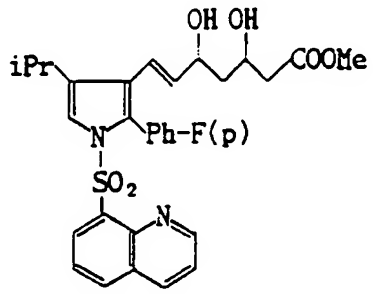
(2) 2-(4-Fluorophenyl)-3-formyl-4-isopropyl-1-(8-quinolylsulfonyl)-pyrrole 10



Compound 9 (7.02 g) is reacted with quinoline-8-sulfonylchloride and treated according to Example 1 (2) to (4) to give 5.63 g (Yield : 78.1%) of compound 10. mp. 157-158 °C

Anal Calcd. (%) for $C_{23}H_{19}N_2SFO_3$					
	C, 65.39;	H, 4.53;	N, 6.63;	S, 7.59;	F, 4.50
Found	C, 65.50;	H, 4.64;	N, 6.67;	S, 7.57;	F, 4.24

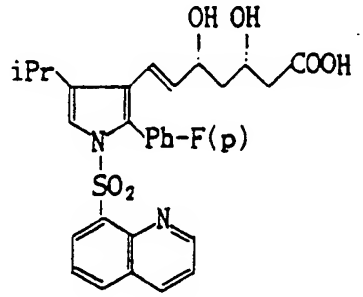
(3) Methyl 7-[2-(4-fluorophenyl)-4-isopropyl-1-(8-quinolinesulfonyl)pyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ib-15)



Compound 10 (5.36 g) is reacted according to Example 14 (1) to (3) to give 0.19 g (Yield : 84.8%) of compound (Ib-15).

Anal Calcd. (%) for $C_{30}H_{31}N_2SFO_6 \cdot 0.5H_2O$					
	C, 62.60;	H, 5.60;	N, 4.87;	S, 5.57;	F, 3.30
Found	C, 62.60;	H, 5.55;	N, 4.78;	S, 5.47;	F, 2.76

(4) 7-[2-(4-Fluorophenyl)-4-isopropyl-1-(8-quinolinesulfonyl)pyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenoic acid (Ia-15)

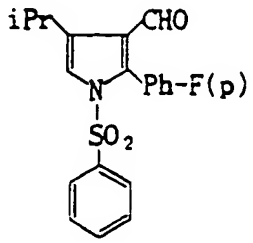


Compound (Ib-15) 0.14 g is reacted according to Example 14 (4) to give 0.13 g (Yield : 94.9%) of compound (Ia-15).

Anal Calcd. (%) for $C_{29}H_{29}N_2SFO_6 \cdot 0.6H_2O$					
	C, 61.82;	H, 5.40;	N, 4.97;	S, 5.69;	F, 3.37
Found	C, 61.64;	H, 5.40;	N, 4.90;	S, 5.76;	F, 3.56

Example 16

(1) 2-(4-Fluorophenyl)-3-formyl-4-isopropyl-1-phenylsulfonylpyrrole 11

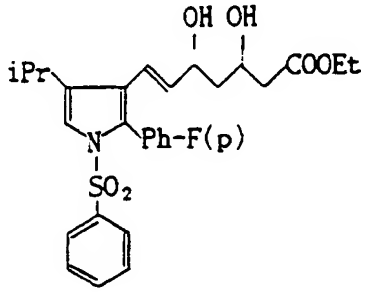


Compound 11 (1.03 g, Yield : 94.3%) is prepared by the reaction of 0.769 g of methyl 4-isopropyl-2-(4-fluorophenylpyrrole)-3-carboxylate with benzenesulfonyl chloride.

NMR ($CDCl_3$) δ :

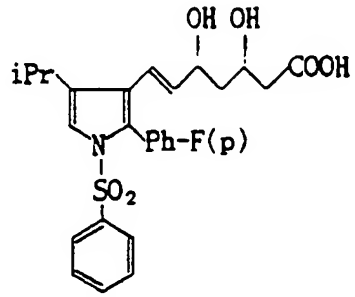
1.25 (d, J=7,6Hz); 3.37 (septet, J=7Hz, 1H); 7.08 (m, 4H); 7.27-7.62 (m, 6H); 9.36 (s, 1H)

(2) Ethyl 7-[2-(4-fluorophenyl)-4-isopropyl-1-phenylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ib-16)



Compound (Ib-16) 0.185 g (Yield : 76.8%) is prepared by the reaction of the compound 11 in the same manner as Example 15 (3).

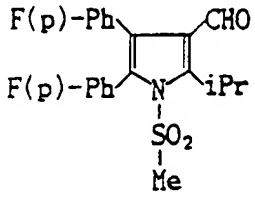
(3) 7-[2-(4-Fluorophenyl)-4-isopropyl-1-phenylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenoic acid (Ia-16)



Compound (Ib-16) is reacted according to Example 15 (4) to give 0.134 g (Yield : 78.6%) of compound (Ia-16).

Example 17

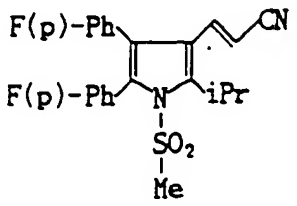
(1) 4,5-Di-(4-fluorophenyl)-3-formyl-2-isopropyl-1-methylsulfonylpyrrole 12



A mixture of 0.53 g (3.4 mmol) of ethyl isobutyrylacetate, 1.52 g (5.4 mmol) of 2-amino-2-(4-fluorophenyl)-4'-fluoroacetophenone, 1.28 ml of acetic acid, 0.46 g of sodium acetate, and 0.88 ml of water is reacted according to Example 1 (1) to (4) to give 1.69 g (Yield : 89.4 %) of compound 12. mp. 213-214 °C

Anal Calcd. (%) for $C_{21}H_{19}NSF_2O_3$					
	C,62.52;	H,4.75;	N,3.47;	S,7.95;	F,9.42
Found	C,62.65;	H,4.91;	N,3.47;	S,7,87;	F,9.20

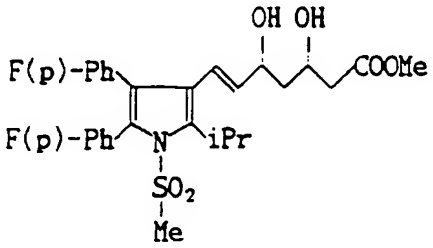
(2) β-[4,5-Di-(4-fluorophenyl)-2-isopropyl-1-methylsulfonylpyrrol-3-yl]-(E)-acrylonitrile 13



Compound 12 (1.68 g, 4.2 mmol) is reacted according to Example 14 (2) to give 0.59 g (Yield : 47.2%) of compound 13. mp. 205-206 °C

Anal Calcd. (%) for $C_{23}H_{20}N_2SF_2O_2$					
	C,64.77;	H,4.73;	N,6.57;	F,8.91;	S,7.52
Found	C,64.92;	H,4.84;	N,6.59;	F,8.71;	S,7.73

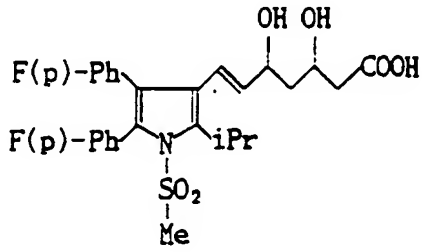
(3) Methyl 7-[4,5-Di-(4-fluorophenyl)-2-isopropyl-1-methylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ib-17)



Compound 13 is reacted according to Example 1 (7) to (9) to give 0.18 g (yield : 81.8%) of compound (Ib-17). mp.127-128°C

Anal Calcd. (%) for $C_{28}H_{31}NSF_2O_6 \cdot 0.2H_2O$					
	C,61.01;	H,5.74;	N,2.54;	S,5.82;	F,6.89
Found	C,60.88;	H,5.67;	N,2.58;	S,6.05;	F,6.83

(4) 7-[4,5-Di-(4-fluorophenyl)-2-isopropyl-1-(methylsulfonyl)pyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenoic acid (Ia-17)

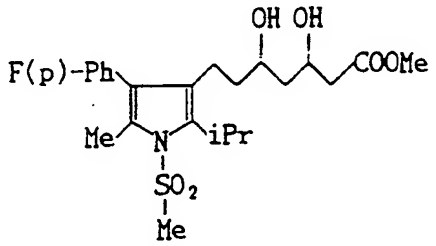


Compound (Ib-17) 0.14 g (0.25 mmol) is reacted according to Example 1 (10) to give 0.12 g (Yield : 88.2%) of compound (Ia-17). mp. 157-159 °C (dec.)

Anal Calcd. (%) for $C_{27}H_{29}NSF_2O_6$					
	C,60.78;	H,5.48;	N,2.63;	S,6.01;	F,7.12
Found	C,60.48;	H,5.58;	N,2.69;	S,6.20;	F,7.41

Example 18

(1) Methyl-7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-(methylsulfonyl)pyrrol-3-yl]-(3R*,5R*)-dihydroxyheptanate (Ib'-14)

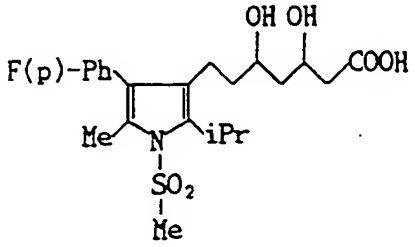


A suspension of 0.17 g of compound (Ib-14), 10 ml of methanol, and 40 mg of 10% Pd-C is shaken under atmospheric pressure at room temperature under hydrogen atmosphere for 6 hours. After Pd-C has been filtered off, the residue is subjected to column chromatography (silica gel), eluting with methylene chloride/ethyl acetate (3/1) to give 0.15 g (Yield : 88.2%) of compound (Ib'-14) as oil.

NMR ($CDCl_3$) δ :

1.26 (m, 2H); 1.39 (d, J=7.6Hz, 6H); 2.22 (s, 3H); 2.40 (d, J=5.6Hz, 2H); 2.59 (m, 2H); 3.14 (s, 3H); 3.64 (m, 1H); 3.71 (s, 3H); 3.78 (m, 1H); 4.11 (m, 1H); 7.13 (m, 4H)

(2) 7-[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-1-(methylsulfonyl)pyrrol-3-yl]-(3R*,5R*)-dihydroxy-heptanoic acid (Ia'-14)



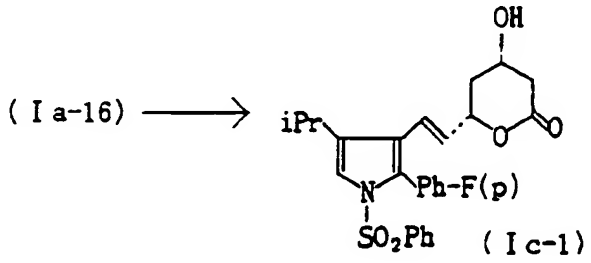
Compound (Ib'-14) 0.16 g is reacted according to Example 1 (10) to give 0.13 g (yield : 83.9%) of compound (Ia'-14) as a powder.

NMR ($CDCl_3$) δ :

1.28 (m, 2H); 1.38 (d, J=7.4Hz, 6H); 2.22 (s, 3H); 2.45 (d, J=6.6Hz, 2H) 2.55 (m, 2H); 3.15 (s, 3H); 3.69 (m, 1H); 3.79 (m, 1H); 4.12 (m, 1H); 7.14 (m, 4H)

Example 19

(E)-6(S*)-[2-[1-Phenylsulfonyl-2-(4'-fluorophenyl)-4-isopropyl-1H-pyrrol-3-yl]ethenyl]-4(R*)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (Ic-1)



Compound (Ia-16) obtained in Example 16 (3) is left at room temperature for 80 days and purified by column chromatography (silica gel), eluting with methylene chloride/methanol (10/1) to give resinous lactone (Ic-1). Yield : 53.7 %

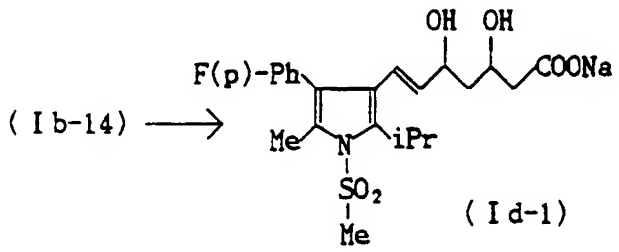
NMR ($CDCl_3$) δ :

1.24 (d, J=7Hz, 3H); 1.26 (d, J=7Hz, 3H); 1.55-1.92 (m, 2H); 2.60 (m, 2H); 4.27 (brs, 1H); 5.01 (m, 1H); 5.54 (dd, J=16,7Hz, 1H); 6.14 (d, J=16 Hz, 1H); 6.98 (m, 5H); 7.24-7.60 (m, 8H)

IR ($CHCl_3$) ν cm^{-1} : 1725, 1370, 1170

Example 20

Sodium 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-methylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Id-1)

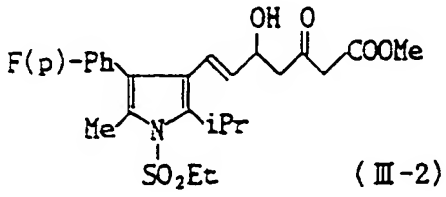


To a solution of 0.185 g (0.396 mmol) of compound (Ib-14) obtained in Example 14 (3) in 4 ml of methanol a solution of 3.96 ml (0.396 mmol) of 0.1N-NaOH is added. The mixture is stirred at room temperature for 1 hour and concentrated under reduced pressure to remove methanol. To the residue 15 ml of water is added, and the solution is freeze-dried to give 0.184 g (Yield : 95.3%) of compound (Id-1) as powder. mp.~167°C

Anal Calcd. (%) for $C_{22}H_{27}NSFNaO_6 \cdot 0.75H_2O$					
	C,54.04;	H,5.87;	N,2.86;	S,6.56;	Na,4.70
Found	C,53.81;	H,5.81;	N,3.04;	S,6.93;	Na,4.84

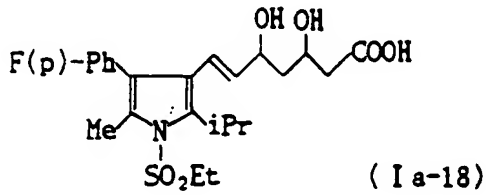
Example 21

(1) Methyl 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-ethylsulfonylpyrrol-3-yl]-5-hydroxy-3-oxo-(E)-6-heptenate (III-2)



β-[4-(4-Fluorophenyl)-2-isopropyl-5-methylpyrrol-3-yl]-(E)-acrylonitrile (1.34 g, 5.0 mmol) is reacted with 0.71 g (5.5 mmol) of ethanesulfonyl chloride and treated according to Example 1 (6) to (7) to give 0.75 g (Yield : 63.6%) of 3-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-ethylsulfonylpyrrol-3-yl-(E)-propenal (II-2). To a suspension of 0.26 g (6.5 mmol) of 60 % NaH in 6 ml of anhydrous THF a solution of 0.70 g (6.0 mmol) of methyl acetoacetate in 6 ml of anhydrous THF is added dropwise under nitrogen atomosphere for 10 minutes. The mixture is stirred at the same temperature for 15 minutes, and 3.75 ml (6.0 mmol) of 1.6M n-BuLi in n-hexane is added dropwise for 5 minutes thereto. The solution is stirred for further 30 minutes, and a solution of compound (II-2) in 15 ml of anhydrous THF is added dropwise thereto. The mixture is treated according t Example 1 (8) to give 0.44 g (Yield : 45.7%) of compound (III-2) as a syrup.
NMR ($CDCl_3$) δ :
1.37 (dd, 3H, J=5Hz;); 1.38 (d, 3H, J=5Hz); 2.23 (s, 3H); 2.51 (d, 2H, J=5.6Hz;); 3.43 (s, 2H); 3.82 (m, 1H); 4.46 (s, 2H); 4.95 (dd, 1H, J= 6.4, 16Hz); 6.61 (dd, 1H, J=1.4,16Hz); 6.96-7.46 (m, 9H)

(2) 7-[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-(1-ethylsulfonyl)pyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ia-18)

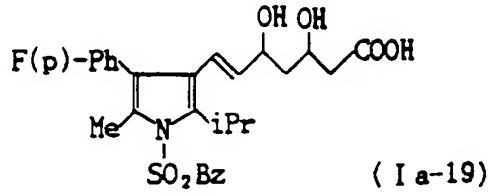


(I a-18)

Compound (III-2) (0.43 g, 0.9 mmol) is reacted according to Example 1 (9) to (10) to give 0.21 g (Yield : 98.1%) of compound (Ia-18) as a powder.
NMR ($CDCl_3$) δ :
1.34 (t, 3H, J=7.4Hz;); 1.37 (d, 6H, J=7Hz); 2.48 (d, 2H, J=6.4Hz;); 3.29 (q, 2H, J=7.4Hz;); 3.82 (m, 1H); 4.14 (brs, 1H); 4.32 (brs, 1H); 4.99 (dd, 1H, J=6.2,16Hz;); 6.58 (dd, 1H, J=0.8,16Hz;); 7.0-7.90 (m, 4H)

Example 22

7-[4-(4-Fluorophenyl)-2-isopropyl-5-methyl-(1-benzylsulfonyl)pyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (Ia-19)

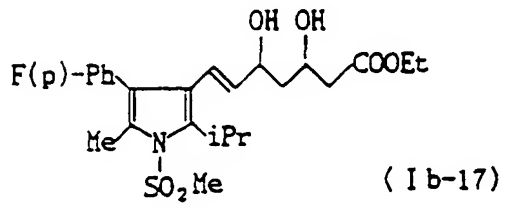


(I a-19)

β-[4-(4-Fluorophenyl)-2-isopropyl-5-methylpyrrol-3-yl]-(E)-acrylonitrile (2.03g, 7.6 mmol) is reacted with 1.50 g (7.9 mmol) of α-toluenesulfonyl chloride and treated according to in Example 21 to give 0.19 g (Yield : 100%) of compound (Ia-19) as a powder.
NMR ($CDCl_3$) δ :
1.36 (dd, 6H, J=1.2,7.2Hz); 2.49 (d, 2H, J=6Hz); 3.81 (m, 1H); 4.18 (brs, 1H); 4.33 (brs, 1H); 4.46 (s, 2H); 4.98 (dd, 1H, J=6.5, 16Hz); 6.57 (dd, 1H, J=1,16Hz); 6.92-7.45 (m, 9H)

Example 23

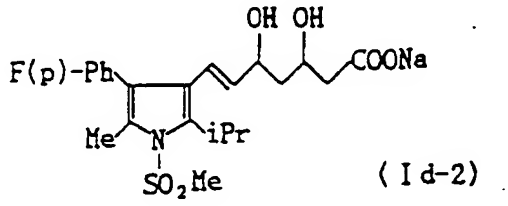
(1) (+) Ethyl 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-(1-methylsulfonyl)pyrrol-3-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (Ib-17)



(I b-17)

Compound 8 obtained in Example 14 (2) is treated according to Example 1 (7) to (9) to give ethyl 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-1-methylsulfonylpyrrol-3-yl]-(3R*,5S*)-dihydroxy-(E)-6-heptenate (the racemate of the compound (Ib-17)). The obtained racemate (82.80 g) is subjected to racemic resolution on HPLC (High Performance Liquid Chromatography) to give 23.8 g of compound (Ib-17) optical purity 98.6%).
$[\alpha]_D^{25}$ =+13.9±0.5° (C=1.012, in dichloroethane)

(2) (+) Sodium 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-(1-methylsulfonyl)pyrrol-3-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (Id-2)



(I d-2)

To a solution of 23.22 g (0.0482 mol) of compound (Ib-17) in 900 ml of ethanol 463 ml (0.0468 mol) of 0.1 N-NaOH is added at room temperature, and the mixture is stirred for 2 hours. After removal of ethanol as a azeotrope under reduced pressure at 35 °C a substance is obtained. The substance is mixed with further 300 ml of ether for crystallization to give 22.54 g (Yield : 91.4%) of compound (Id-2).

Anal Calcd. (%) for $C_{22}H_{27}NO_6SFNa \cdot 2H_2O$						
	C,51.66;	H,6.11;	N,2.74;	S,6.27;	F,3.71;	Na,4.49
Found	C,51.79;	H,6.17;	N,2.84;	S,6.12;	F,3.49;	Na,4.63

NMR ($CDCl_3$) δ :
1.33 (s, 3H); 1.37 (s, 3H); 2.15 (s, 3H); 2.24 (m, 2H); 3.36 (s, 3H); 3.72 (m, 2H); 4.21 (m, 1H); 4.98 (dd, J=16,7Hz, 1H); 6.62 (d, J=16Hz,1H); 7.14 (m, 4H)
[α]D=+28.3±0.7° (C=1.010, 25.5°C, water)

Evaluation of biological activity

Experiment

The HMG-CoA reductase inhibitory effect

(1) Preparation of rat liver microsomes

Sprague-Dawley rats, which were in free access to an ordinary diet containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsomes, which were then purified according to Kuroda et al., Biochem. Biophys. Act, 486, 70 (1977). The microsamal fraction obtained by centrifugation at 105000×g was washed once with a buffered solution containing 15mM nicotinamide and 2mM magnesium chloride (in a 100mM potassium phosphate buffer, pH 7.4). It was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The thus obtained homogenate was cooled down to and kept at -80 °C.

(2) Measurement of the HMG-CoA reductase inhibitory activities

The rat liver microsomes (100 μℓ), which were preserved at -80°C, were fused at 0°C and diluted with 0.7ml of a cold potassium phosphate buffer (100mM, pH7.4). This was mixed with 0.8ml of 50mM EDTA (buffered with the aforementioned potassium phosphate buffer) and 0.4 ml of 100mM dithiothreitol solution (buffered with the aforementioned potassium phosphate buffer), and the mixture was kept at 0°C. The microsome solution (1.675 ml) was mixed with 670 μℓ of 25mM NADPH (buffered with the aforementioned potassium phosphate buffer), and the solution was added to the solution of 0.5mM [3^{-14}C]HMG-CoA (3mCi/mmol). The sodium salt of the test compound in a potassium phosphate buffer (5 μl) was added to the mixture of microsomes and HMG-CoA (45 μl). The resulting mixture was incubated at 37 °C for 30 minutes and cooled. After termination of the reaction by addition of 10 μℓ of 2N-HCl, the mixture was incubated again at 37°C for 15 minutes and then 30 μℓ of this mixture was applied to thin-layer chromatography [silica gel, 0.5mm thick (Merck AG, Art 5744)]. The chromatograms were developed in toluene/acetone (1/1) and the sections, whose Rf value was between 0.45 to 0.6, were scraped. The obtained products were put into a vial containing 8 ml of scintillator to measure the specific radio-activity with a scintillation counter. The results are shown in Table 4.

Table 4

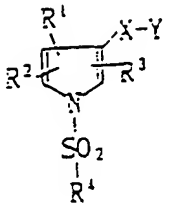
Test Compound	HMG-CoA reductase inhibitory activities*
Ia-10	263
Ia-17	293
Ia-18	228
Ia-19	105
Id-2	418
Mevinolin Na	100

* : The activities of the present compounds are shown comparatively, based on the assumption that the activity of Mevinolin (sodium salt) as reference drug is 100.

From the above data, it is evident that the compounds of the present invention exhibit superior activities to Mevinolin in HMG-CoA reductase inhibition.

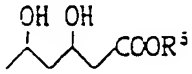
Claims

1. A compound represented by the formula (I):

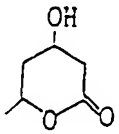


(I)

wherein R^1, R^2, and R^3 each is independently hydrogen, optionally substituted lower alkyl, or optionally substituted aryl with the proviso that one of the substituents R^1, R^2 and R^3 is isopropyl; R^4 is lower alkyl, aralkyl, aryl, or heteroaryl, each of which is optionally substituted; X is vinylene or ethylene; Y is



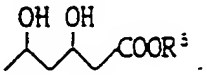
or



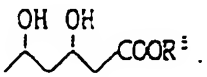
where R^5 is hydrogen, lower alkyl, aryl, aralkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt, wherein the term "optionally substituted lower alkyl" refers to a straight or branched chain C_1 to C_6 alkyl, which may be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, lower alkoxyamino and cyano;
and the optional substituents of the aryl, aralkyl and heteroaryl group are from 1 to 3 substituents independently selected from the group consisting of a straight or branched chain C_1 to C_6 alkyl, halogen, amino, and cyano.

2. The compound claimed in claim 1, wherein X is vinylene.

3. The compound claimed in claim 1, wherein Y is



4. The compound claimed in claim 1, wherein X is vinylene and Y is



5. The compound claimed in claim 1, wherein said compound takes an optically active form.

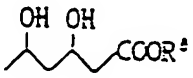
6. The compound claimed in claim 1, namely (+) sodium 7-[4-(4-fluorophenyl)-2-isopropyl-5-methyl-(1-methylsulfonyl)pyrrol-3-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate.

7. A pharmaceutical composition comprising a pharmacologically effective amount of the compound claimed in any of claims 1 to 6, together with a carrier, diluent, and/or excipient.

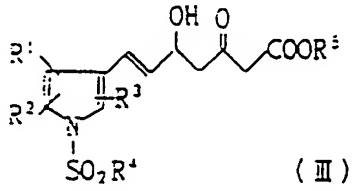
8. A pharmaceutical composition claimed in claim 7, which is effective as an HMG-CoA reductase inhibitor.

9. A process for preparing a compound of the formula (I) as defined in claims 1 to 6, which process comprises either

(a) in order to prepare a compound of the formula (I) wherein Y is



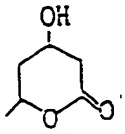
reacting a compound of the formula (III):



(Ⅲ)

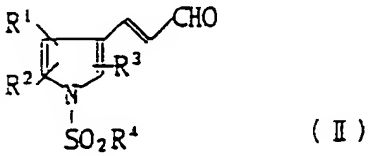
wherein R^1, R^2, R^3, R^4, and R^5 each has the same meaning as defined above, with diethylmethoxyborane and $NaBH_4$, and if desired, subjecting the resulting compound to reduction, or

(b) in order to prepare a compound of formula (I) wherein Y is



subjecting the resulting compound of step (a) to hydrolysis, salt formation and/or cyclization.

10. A process for preparing compound (III) as the starting compound of a process as claimed in claim 9 which comprises reacting a compound of the formula (II):



(Ⅱ)

wherein R^1, R^2, R^3, and R^4 each has the same meaning as defined above, with a compound of the formula (IV):

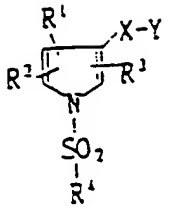
$$CH_3COCH_2COOR^5 \qquad (IV)$$

wherein R^5 has the same meaning as defined above.

11. A method for the preparation of a pharmaceutical composition according to claim 7 or 8 comprising combining a compound as defined in any one of claims 1 to 6 with a pharmaceutically acceptable carrier, diluent and/or excipient.

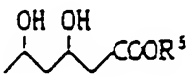
Patentansprüch

1. Verbindung der Formel (I)

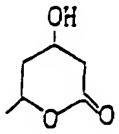


(I)

in der R^1, R^2 und R^3 unabhängig voneinander ein Wasserstoffatom, einen gegebenenfalls substituierten Niederalkylrest oder gegebenenfalls substituierten Arylrest bedeuten, mit der Maßgabe, daß einer der Substituenten R^1, R^2 und R^3 eine Isopropylgruppe bedeutet; R^4 einen Niederalkyl-, Aralkyl-, Aryl- oder Heteroarylrest bedeutet, die gegebenenfalls substituiert sind, X eine Vinylen- oder Ethylengruppe bedeutet, Y einen Rest



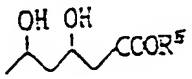
oder



bedeutet, wobei R^5 ein Wasserstoffatom, einen Niederalkyl-, Aryl- oder Aralkylrest oder ein Kation bedeutet, das ein ungiftiges, pharmazeutisch verträgliches Salz bilden kann, wobei der Begriff -gegebenenfalls substituierter Niederalkylrest" sich auf einen gerad- oder verzweigtkettigen C_{1-6}-Alkylrest bezieht, der durch 1 bis 3 Substituenten substituiert sein kann, die unabhängig voneinander aus Halogenatomen, Niederalkoxyaminoresten und Cyanogruppen ausgewählt sind, und die wahlweisen Substituenten des Aryl-, Aralkyl- und Heteroarylrests 1 bis 3 Substituenten sind, die unabhängig voneinander aus gerad- oder verzweigtkettigen C_{1-6}-Alkylresten, Halogenatomen, Amino- und Cyanogruppen ausgewählt sind.

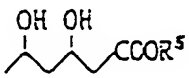
2. Verbindung nach Anspruch 1, in der X eine Vinylengruppe bedeutet.

3. Verbindung nach Anspruch 1, in der Y einen Rest



bedeutet.

4. Verbindung nach Anspruch 1, in der X eine Vinylengruppe und Y einen Rest



bedeutet.

5. Verbindung nach Anspruch 1, wobei die Verbindung in optisch aktiver Form vorliegt.

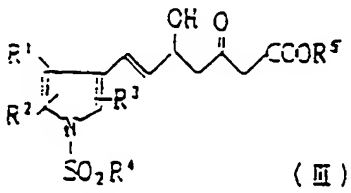
6. Verbindung nach Anspruch 1, nämlich Natrium-(+)-7-[4-(4-Fluorphenyl)-2-isopropyl-5-methyl-(1-methylsulfonyl)pyrrol-3-yl]-(3R,5S)-dihydroxy-(E)-6-heptenat.

7. Arzneimittel, umfassend eine pharmazeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 6 im Gemisch mit einem Träger, Verdünnungsmittel und/oder Arzneimittelträger.

8. Arzneimittel nach Anspruch 7, das als HMG-CoA-Reduktase-Hemmer wirksam ist.

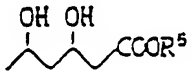
9. Verfahren zur Herstellung einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 6, wobei das Verfahren entweder

(a) die Umsetzung einer Verbindung der Formel (III)



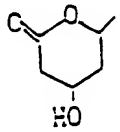
(III)

in der R^1, R^2, R^3, R^4 und R^5 die vorstehend gegebenen Bedeutungen haben, mit Diethylmethoxyboran und Natriumborhydrid und gegebenenfalls die Reduktion der erhaltenen Verbindung umfaßt, um eine Verbindung der Formel (I) herzustellen, in der Y einen Rest



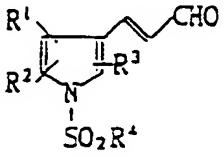
bedeutet, oder

(b) die Hydrolyse, Salzbildung und/oder Cyclisierung der in Stufe (a) erhaltenen Verbindung umfaßt, um eine Verbindung der Formel (I) herzustellen, in der Y einen Rest



bedeutet.

10. Verfahren zur Herstellung einer Verbindung (III), der Ausgangsverbindung eines Verfahrens nach Anspruch 9, das die Umsetzung einer Verbindung der Formel (II)



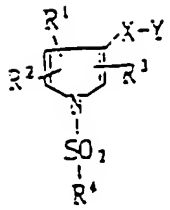
(II)

in der R^1, R^2, R^3 und R^4 die vorstehend gegebenen Bedeutungen haben, mit einer Verbindung der Formel $CH_3COCH_2COOR^5$ (IV), in der R^5 die vorstehend gegebene Bedeutung hat, umfaßt.

11. Verfahren zur Herstellung eines Arzneimittels nach Anspruch 7 oder 8, umfassend die Vereinigung einer Verbindung nach einem der Ansprüche 1 bis 6 mit einem pharmazeutisch verträglichen Träger, Verdünnungsmittel und/oder Arzneimittelträger.

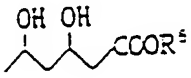
Revendicati ns

1. Composé représenté par la formule (I) :

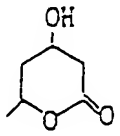


(I)

dans laquelle R^1, R^2 et R^3 représentent chacun indépendamment de l'hydrogène, un groupe alkyle inférieur éventuellement substitué ou un groupe aryle éventuellement substitué, à la condition que l'un des substituants R^1, R^2 et R^3 représente un groupe isopropyle, R^4 représente un groupe alkyle inférieur, aralkyle, aryle ou hétéroaryle, chacun de ces groupes étant éventuellement substitué, X représente un groupe vinylène ou éthylène, Y représente un groupe :



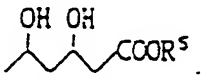
ou



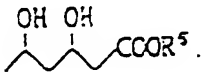
où R^5 représente de l'hydrogène, un groupe alkyle inférieur, aryle, aralkyle ou un cation pouvant former un sel pharmaceutiquement acceptable non toxique, l'expression "groupe alkyle inférieur éventuellement substitué" se référant à un groupe alkyle en C_1 à C_6 à chaîne droite ou ramifiée, qui peut être substitué par 1 à 3 substituants choisis indépendamment dans le groupe comprenant les halogènes, alcoxyamino inférieurs et cyano, et les éventuels substituants des groupes aryle, aralkyle et hétéroaryle sont de 1 à 3 substituants choisis indépendamment dans le groupe comprenant les alkyles en C_1 à C_6 à chaîne droite ou ramifiée, halogènes, amino et cyano.

2. Composé suivant la revendication 1, dans lequel X représente du vinylène.

3. Composé suivant la revendication 1, dans lequel Y représente



4. Composé suivant la revendication 1, dans lequel X représente du vinylène et Y représente



5. Composé suivant la revendication 1, dans lequel ledit composé est sous une forme optiquement active.

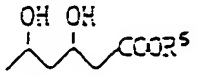
6. Composé suivant la revendication 1, à savoir le (+) 7-[4-(4-fluorophényl)-2-isopropyl-5-méthyl-(1-méthylsulfonyl)pyrrol-3-yl]-(3R,5S)-dihydroxy-(E)-6-heptènate de sodium.

7. Composition pharmaceutique comprenant une quantité pharmacologiquement efficac du composé suivant l'une quelconque des revendications 1 à 6, en même temps qu'avec un support, diluant et/ou excipient.

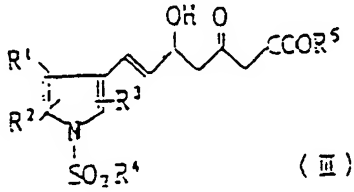
8. Composition pharmaceutique suivant la revendication 7, qui est efficace comme inhibiteur de l'HMG-CoA réductase.

9. Procédé de préparation d'un composé de la formule (I) suivant l'une quelconque des revendications 1 à 6, lequel procédé comprend soit

(a) afin de préparer un composé de la formule (I) dans laquelle Y représente

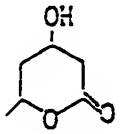


la réaction d'un composé de la formule (III) :



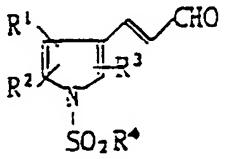
(III)

où R^1, R^2 R^3, R^4 et R^5 ont chacun la même signification que donnée précédemment, avec du diéthylméthoxyborane et du $NaBH_4$ et, suivant les nécessités, la réduction du composé résultant, soit
(b) afin de préparer un composé de la formule (I) dans laquelle Y représente



le traitement du composé résultant de l'étape (a) en le soumettant à une hydrolyse, formation de sel et/ou cyclisation.

10. Procédé de préparation d'un composé (III) comme composé de départ d'un procédé suivant la revendication 9, qui comprend la réaction d'un composé de la formule (II) :



(II)

où R^1, R^2 R^3 et R^4 ont chacun la même signification que donnée précédemment, avec un composé de la formule (IV) :

$$CH_3COCH_2COOR^5 \qquad (IV)$$

dans laquelle R^5 a la même signification que donnée précédemment.

11. Procédé de préparation d'une composition pharmaceutique suivant l'une ou l'autre des revendications 7 et 8, comprenant la combinaison d'un composé suivant l'une quelconque des revendications 1 à 6 avec un support, diluant et/ou excipient pharmaceutiquement acceptable.